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DRUG SAFETY EVALUATION

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Drug safety evaluation of parathyroid hormone for hypocalcemia in patients with hypoparathyroidism

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ABSTRACT

Introduction: Hypoparathyroidism is a rare disorder characterized by low serum calcium levels and high serum phosphate levels, and low or inappropriately normal levels of parathyroid hormone (PTH). This disease is commonly treated with calcium supplements and active vitamin D metabolites or analogues, but large doses of these supplements are often utilized to relieve the symptoms caused by hypocalcemia, without guarantee of a physiological normalization of calcium-phosphate homeostasis.

Areas covered: Several studies have investigated replacement therapy with recombinant human PTH [rhPTH (1-84) and rhPTH (1-34)] for subjects with hypoparathyroidism. In 2015, The Food and Drug Administration (FDA) approved, in the United States, rhPTH (1–84), named Natpara®, a bioenginerred rhPTH, for the management of chronic hypoparathyroidism not well controlled with conventional therapy. This article evaluates the safety and tolerability of rhPTH (1–84) in patients with chronic hypoparathyroidism, and also describes the studies conducted so far on rhPTH (1-34) used for chronic hypoparathyroidism.

Expert opinion: The research done in this field has shown that replacement treatment with rhPTH is an attractive option for subjects with hypoparathyroidism who are unable to maintain stable and safe serum and urinary calcium levels. However, since therapy with rhPTH is a long-term management option in hypoparathyroidism, more long-term safety data are needed.

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1. Introduction

Hypoparathyroidism is a rare disorder characterized by low serum calcium levels and high serum phosphate levels due to absent or inappropriately low parathyroid hormone (PTH) levels [1]. This disorder can be acquired or hereditary. It results from a surgical procedure in approximately 75% of patients and in the remainder is due to genetic, autoimmune, or idiopathic etiologies [1,2]. Hypoparathyroidism is commonly treated with calcium supplements and active vitamin D metabolites or analogs, but often large doses of these supplements are utilized to relieve the symptoms caused by hypocalcemia, without guarantee of a physiological normalization of calcium-phosphate homeostasis [3]. Even when conventional therapy is able to normalize serum calcium concentrations, patients can suffer from reduced quality of life, muscle complaints (including fatigue and weakness), and anxiety and tendency to depression, in addition to the risks of many long-term complications, such as nephrolithiasis, nephrocalcinosis, renal impairment, cataracts, and cerebral calcifications [3].

2. A new era for chronic management of hypoparathyroidism: PTH peptides

Over the past two decades, several studies have investigated replacement therapy with recombinant human PTH [rhPTH (1-84)] and with the N-terminal PTH fragment, teriparatide, [rhPTH (1-34)]. These drugs are administered by subcutaneous injection and have different pharmacokinetics; rhPTH (1-84) is administered once daily, while rhPTH (1-34) is administered by single/multiple injection/s per day or via pump delivery [4,5]. In 2015, The Food and Drug Administration (FDA) approved rhPTH (1-84), named Natpara®, a bioenginerred rhPTH, for the management of hypoparathyroidism, only in the USA [6]. It is produced by recombinant DNA technology using a strain of *Escherichia coli*. A recent guideline, published in 2016, recommends taking into consideration rhPTH (1-84) therapy in any patient with well-established chronic hypoparathyroidism of any etiology, except for autosomal dominant hypocalcemia (ADH) type 1 and, in particular, in case of: variable and inconstant control of the serum calcium with frequent episodes of hypo- and hypercalcemia; oral calcium/vitamin D medications required to control the serum calcium or symptoms that exceed 2.5 g of calcium or >1.5 µg of active vitamin D; hypercalciuria, renal stones, nephrocalcinosis, stone risk, or reduced creatinine clearance or estimated glomerular filtration rate (eGFR <60m/min), hyperphosphatemia and/or calcium-phosphate product that exceeds 55 mg^2dL^2 (4.4 $mmol^2L^2$); gastrointestinal tract disorder that is associated with malabsorption; and, finally, reduced quality of life [3]. Natpara® has not been studied in patients affected by hypoparathyroidism

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Box 1. Drug summary.

Drug name (generic)	Recombinant human PTH (1-84)
Phase (for indication under discussion)	Launched
Indication (specific to discussion)	Hypoparathyroidism
Pharmacology description/ mechanism of action	Parathyroid hormone receptor 1 agonist
Route of administration	Subcutaneous injection
Chemical structure	
Pivotal trial(s)	REPLACE, REPEAT; RACE (active, not recruiting)

with calcium-sensing receptor (CaSR) mutations, because these patients may have normal levels of PTH but hypocalcemia, representing a steady state of the abnormally sensitive CaSR. In these cases, future therapies might employ calcilytics, which directly modulate the CaSR. In particular, these molecules bind in the HH (heptahelical) (see Box 1) domain and suppress CaSR signaling, and at the level of parathyroid glands, calcilytics promote PTH secretion by reversing the inhibitory action of the CaSR. Several classes of calcilytics, as negative modulators of the CaSR, have been developed, and therapeutic attempts using calcilytics to treat ADH type 1, caused by heterozygous activating mutations in the CASR, are currently under investigation [7].

2.1. rhPTH (1-84) hormone replacement therapy in chronic hypoparathyroidism and its drug safety evaluation

rhPTH (1-84) is a molecule of 84 amino acids, identical to the full-length human protein. It is produced by recombinant DNA technology using a strain of *Escherichia coli* [6].

Therapy with rhPTH (1-84) increases plasma calcium concentrations in a dose-related manner. After a single subcutaneous injection, the mean peak serum calcium level is reached between 10 and 12 h. Then, the increase of serum calcium above baseline is maintained for more than 24 h. At 12 h, the maximum mean increases of serum calcium reported are about 0.5 mg/dl and 0.7 mg/dl from baseline, respectively, with a dose of 50 and 100 mcg [6]. The drug is supposed to be administered as a once-a-day subcutaneous injection in the thigh with a starting dose of 50 mg. At the time of initiation of therapy, daily dose of active vitamin D is reduced by 50%, and serum calcium levels are monitored once or twice a week. According to a predefined schedule, daily dose of active vitamin D and calcium supplements may be further reduced according to serum calcium measurement. The dose of rhPTH (1-84) can be down-titrated to a daily dose of 25 mg or up-titrated to a daily injection of either 75 or 100 mg [6].

The apparent terminal half-life ($t_{1/2}$) is 3.02 and 2.83 h, respectively, for doses with 50 and 100 mcg. The peak plasma concentrations (mean T_{max}) of rhPTH (1-84), for doses of 50 and 100 mcg in patients with hypoparathyroidism, occurs within 5–30 min, followed by a second, usually smaller, peak at 1–2 h. The area under the curve (AUC) increased in a dose-proportional manner from 50 to 100 mcg. The bioavailability is 53%, and *in vitro* and *in vivo* studies have shown that the clearance of PTH hormone is mostly by a hepatic process and, to a lesser extent, by renal process [6]. No dose adjustment for this drug is recommended in patients with mild to moderate hepatic impairment, and no studies have been conducted in patients with severe renal impairment or in renal impairment patients on dialysis [6].

It has been demonstrated that this drug permits major reductions in the need for calcium and active vitamin D metabolites or analog supplements, maintaining normal calcium concentrations in patients affected by chronic hypoparathyroidism. So far, the studies conducted on rhPTH (1-84) as hormone replacement therapy for chronic hypoparathyroidism have shown an improvement of calcium homeostasis, maintaining serum calcium in the normal range, and a trend to the reduction of 24-h calcium excretion, although this last outcome has not always been achieved [8–14]. Some studies also tested the hypothesis that rhPTH (1-84) therapy in chronic hypoparathyroidism could be associated with improvement in quality of life measures. In particular, a study evaluated 69 hypoparathyroid subjects, treated with rhPTH (1-84) for a period of 5 years, through the use of RAND 36-Item Short Form (SF-36) Health Survey, a measure of health-related quality of life, which the subjects completed before and during therapy with rhPTH (1–84) [15]. Most subjects maintained serum calcium values of at least 8.0 mg/dL throughout the study period. The subjects showed significant improvement in the overall score at 2 months that persisted for 5 years. The authors concluded that rhPTH (1-84) therapy is associated with improvement in mental and physical health as determined by the SF-36 metric; however, the limit of this study is that there is not a placebo group [15]. On the other hand, a placebo-controlled study conducted on 62 patients with chronic hypoparathyroidism did not demonstrate improvement in quality of life, although a high frequency of hypercalcemic episodes among these patients may have compromised the potential beneficial effects of reversing the state of PTH insufficiency [16]. Since few data exist characterizing the potential effects of rhPTH therapy to ameliorate quality of life measures, in future studies, tests should be performed to confirm the potential positive association between treatment with rhPTH (1-84) and this important aspect of life for patients with hypoparathyroidism. Therapy with rhPTH (1-84) also promotes the reverse of the state of low bone turnover, typical of hypoparathyroidism, increasing bone turnover, and seems to promote the restoration of normal bone physiology [17]. However, more data are clearly needed in order to understand the long-term effects of rhPTH (1-84) on BMD (bone mineral density) changes, bone quality, and risk of fractures. Finally, this drug has a potential preventive role for other complications including nephrolithiasis, nephrocalcinosis, cataracts, and cerebral calcifications [9–14].

Below, there is a comprehensive analysis of results on drug safety profile found in papers published from 2010 until now. The major findings regarding effects on serum and urinary calcium levels and reduction of calcium and calcitriol supplementation of all clinical studies conducted with rhPTH (1-84) are summarized in Table 1.

Rubin et al. described the use of the rhPTH (1-84) in a fixed dose of 100 µg every other day by subcutaneous injection in

Table 1. The major findings regarding effects on serum and urinary calcium levels and reduction of calcium and calcitriol supplementation of clinical studies conducted with recombinant human parathyroid hormone (rhPTH) (1-84).

Authors and year of publication	Subjects	Type of study	Duration of the study	Main results
Rubin et al. 2010 [10]	30 adults	Open-label every other day rhPTH (1-84) subcutaneous (s.c.) injections (100 µg)	24 months	Decrease of total dose of calcium and calcitriol supplementation. Serum calcium levels and 24-h urinary calcium excretion were mostly unchanged at 24 months.
Sikjaer et al. 2011[9]	62 adults	Double-blind, randomized, placebo-controlled once per day rhPTH (1-84) s.c. injections (100 µg) versus calcium and 1-25$(OH)_2$ D	24 weeks	Decrease of total dose of calcium and calcitriol supplementation. Serum and urinary calcium levels mostly remained stable at 24 weeks.
Cusano et al. 2013 [11]	27 adults	Open-label every other day rhPTH (1-84) s.c. injections (starting dose 100 µg)	4 years	Decrease of total dose of calcium and calcitriol supplementation. Serum and urinary calcium levels mostly remained stable at 4 years.
Mannstad et al. 2013 [12]	134 adults	Double-blind, randomized, placebo-controlled once per day rhPTH (1-84) s.c. injections (starting dose 50 µg) versus calcium and 1-25$(OH)_2$ D	24 weeks	Decrease of total dose of calcium and calcitriol supplementation. Serum and urinary calcium levels remained stable at 24 weeks.
Lakatos et al. 2016 [13]	24 adults	Open-label, flexible-dose extension study of REPLACE once per day rhPTH (1-84) s.c. injections (starting dose 50 µg)	24 weeks	Decrease of total dose of calcium and calcitriol supplementation. Serum and urinary calcium levels remained stable at 24 weeks.
Rubin et al. 2016 [14]	33 adults	Prospective open-label study, every other day rhPTH (1-84) s.c. injections (starting dose 100 µg)	6 years	Decrease of total dose of calcium and calcitriol supplementation. Serum calcium levels: mostly unchanged, and urinary calcium excretion: decreased (urinary calcium excretion fell significantly below pretreatment levels at years 1, 3, and 6).

30 patients with hypoparathyroidism in an open-label study conducted for 24 months. Transient, mild hypercalcemia occurred sporadically, and not time- or dose-dependent; however, blood sampling was performed only 48 h after the last PTH injection, and therefore other episodes with hypercalcemia might have been missed [10].

Sikjaer et al. published the data derived from a randomized, controlled, double-blind study, in which rhPTH (1-84) or placebo was administrated in a fixed dose of 100 μg in 62 patients for 24 weeks [9]. Treatment with rhPTH (1-84) resulted in episodes of hypercalcemia during titration, but, compared with treatment with active vitamin D metabolites, hypercalcemic symptoms reportedly were less pronounced and of shorter duration. Renal function remained stable, and there was no difference between groups in the occurrence of serious adverse effects. Infections, musculoskeletal aches, paresthesias, and headache followed by cardiovascular complaints were the most common complaints described, but only nausea occurred with a significantly higher frequency in the group treated with rhPTH (1-84) than in the placebo group. Eight severe adverse events were described, among which five occurred in the group treated with rhPTH (1-84) and three in the placebo-group. Two significant adverse events, requiring hospitalization, were due to hypercalcemia and hypocalcemia, respectively [9].

Cusano et al. described the effect of 4 years of rhPTH (1-84) treatment, administered at a starting dose of 100 μg subcutaneous every other day, in 27 adults affected by chronic hypoparathyroidism.

Hypercalcemia was uncommon (11 episodes in 8 subjects over 4 years; 1.9% of all values), with most episodes occurring within the first 6 months and resolving with adjustment of supplemental calcium and vitamin D. No hypercalcemic events required hospitalization. Blood sampling was performed 48 h after the last PTH injection. Musculoskeletal, gastrointestinal, and genitourinary complaints were the most common adverse events described. Other adverse events included: two fractures [the fracture sites were: elbow (year 1); toe (year 4)] and one episode of nephrolithiasis [11].

In REPLACE ["Efficacy and safety of recombinant human parathyroid hormone (1-84) in hypoparathyroidism"], a double-blind, placebo-controlled, randomized phase 3 study, 134 patients with chronic hypoparathyroidism were randomly assigned to 50 μg per day of rhPTH (1-84), but could be titrated up from 50 to 75 μg and then 100 μg (weeks 0–5), or placebo for 24 weeks (with a randomization scheme of 2:1, drug:placebo) [12]. The primary end point was the proportion of patients at 24 weeks who achieved a 50% or greater reduction from baseline in their daily dose of oral calcium and active vitamin D with maintenance of the serum calcium. This end point was met in over half of the study subjects and in virtually none of the subjects who received placebo. The overall incidence of adverse events was similar in both groups. Serious adverse events were described in 10 (11%) of the patients in the rhPTH (1-84) group and 4 (9%) in the placebo group. In the group treated with rhPTH (1-84), only one serious adverse event due to hypercalcemia was reported. In both groups, no adverse events regarding cardiovascular or renal manifestations were described. During maintenance period (weeks 16–24), a smaller proportion of patients treated with rhPTH (1-84) reported clinical symptoms associated with hypocalcemia than did those in the placebo group [12].

Subsequently, another study, called REPEAT ["An open-label extension study of parathyroid hormone rhPTH(1-84) in adults with hypoparathyroidism"], has been conducted as a 24-week, open-label, flexible-dose extension study of REPLACE [13]. Patients previously completed or enrolled in REPLACE received rhPTH (1-84), 50 μg/day, escalated to 75 and then to 100 μg/day, if required. Twenty-four patients, of which 16 previously treated with rhPTH (1-84), and 8 rhPTH (1-84)-naïve, were enrolled and completed the study. This extension study did not show serious adverse events, and no patients discontinued because of adverse events. The most frequently reported treatment-emergent adverse events, mild or moderate in severity, such as hypocalcemia, muscle spasms, vitamin D decrease, hypercalcemia, fatigue, headache, and hypocalcemia, were described. In five patients (21%), adverse events occurred related to the drug, and all resolved within 7 days. Three patients had rhPTH (1-84) dose reduction to 50 μg every other day for hypercalcemia. Sustained rhPTH (1-84) efficacy up to 48 weeks was described despite treatment interruption between studies [13].

Rubin et al. have recently published a prospective open-label study of 33 subjects affected by hypoparathyroidism, treated with rhPTH (1-84) administered subcutaneously (starting dose of 100 μg every other day) for a period of 6 years [14]. During the course of this study, a titration schedule in which the dose could be increased or decreased was followed. The dose was adjusted for almost all patients, varying with a dosage of 25, 50, 75, and 100 mcg daily, at time points ranging from 4 months to 5.5 years of treatment (median time of dose change was 3.5 years). The experience with the therapeutic use of PTH for 6 years has demonstrated, although in a small sample, safety regarding the control of calcium homeostasis. Serum calcium levels remained in the lower end of the normal range throughout the 6 years, and urinary calcium excretion fell significantly below pretreatment levels at years 1, 3, and 6. No hypercalcemic events required hospitalization. Moreover, many adverse events, including nausea, headache, musculoskeletal ache, fatigue, dizziness, neurologic, mental and mood, paresthesia, and increased urination, were diminished after the first year of treatment. The most common serious adverse event was hypocalcemia (five times in three patients), and other adverse events included eight fractures (the fracture sites were: wrist and elbow [year 1], toe [year 2], fourth metatarsal [year 3], wrist [year 5], and wrist, leg, and toe [year 6]), in six patients. Other adverse events included three episodes of nephrolithias in three patients [14]. In this study, which is the longest clinical study with rhPTH (1-84) treatment available so far in the management of hypoparathyroidism, lumbar spine BMD increased as did total hip BMD, whereas femoral neck BMD remained stable and the distal one-third radius decreased. On the other hand, bone turnover markers increased significantly, reaching a 3-fold peak above baseline values at 1 year and subsequently declining but remaining higher than pretreatment values [14].

Table 2. Adverse reactions associated with recombinant human parathyroid hormone (rhPTH) (1-84) in subjects with hypoparathyroidism.

	N: 84 subjects %
Paresthesia	31
Hypocalcemia	27
Headache	25
Hypercalcemia	19
Nausea	18
Hypesthesia	14
Diarrhea	12
Vomiting	12
Arthralgia	11
Hypercalciuria	11
Pain in extremity	10
Upper respiratory tract infection	8
Abdominal pain upper	7
Sinusitis	7
Blood 25-hydroxycholecalciferol decreased	6
Hypertension	6

During pregnancy and lactation, no adequate studies in women for the use of rhPTH (1-84) have been carried out, except for some animal studies. Since animal studies are not always predictive of human response and, in fact, the effects of rhPTH (1-84) during pregnancy and breastfeeding are unknown, the drug should be not used in these conditions [6].

Safety and efficacy in patients <18 years of age have not been reported, and the use of this drug is currently to be avoided in case of pediatric and young adult patients with open epiphyses, considering the increased baseline risk for osteosarcoma [18]. Moreover, there are no clinical studies that include a sufficient number of patients aged 65 and over to determine a different response in these subjects compared to younger subjects. Therefore, caution is recommended in increasing the dosage of the drug in elderly individuals [6].

rhPTH (1-84) may trigger the development of antibodies. Among the clinical studies conducted in patients with hypoparathyroidism treated with rhPTH (1-84) for up to 2.6 years, the immunogenicity incidence rate was 16.1% (14/78). Anti-PTH antibodies did not appear to affect efficacy or safety during the clinical trials, but their longer-term impact is unknown. Moreover, it is important to remember that immunogenicity assay results are highly dependent on the sensitivity and specifics of the assay and can be influenced by several factors [6]. No adverse events are correlated with the presence of antibodies [9].

The common adverse reactions associated with rhPTH (1-84) in subjects affected by chronic hypoparathyroidism described in the clinical trials are summarized in Table 2.

2.2. rhPTH (1-34) hormone replacement therapy in chronic hypoparathyroidism and its drug safety evaluation

From 1996 until now, some studies have analyzed varying dose regimens of rhPTH (1-34) for the treatment of chronic hypoparathyroidism, including once-daily and twice-daily subcutaneous injections, and administration pump delivery system in adults and children [19–24]. These studies have shown that rhPTH (1-34) achieved better results in terms of maintaining normal serum calcium compared to conventional therapy. In particular, the studies on injections twice a day of rhPTH (1-34) have shown a good control of calcium concentrations compared with conventional therapy, and less fluctuation in serum calcium levels compared with injections once a day, associated with a total daily PTH dose, markedly reduced. Subsequently, rhPTH (1-34) therapy delivered by an infusion pump showed near normalization of the diurnal rhythm of PTH, calcium and phosphate concentrations, and a significant reduction of 24-h urinary calcium levels compared with twice-a-day injection therapy.

Below, there is a comprehensive analysis of results on drug safety profile among the papers published from 1998 until now. The major findings regarding effects on serum and urinary calcium levels and reduction of calcium and calcitriol supplementation of all clinical studies conducted with rhPTH (1-34) are summarized in Table 3.

A 28-week randomized crossover trial conducted in 17 adult patients with chronic hypoparathyroidism that compared once-daily and twice-daily rhPTH (1-34) regimens reported that four patients had bone pain during the once-daily arm and one patient during the twice-daily arm. Nocturia has been reported in two patients during twice-daily PTH therapy. During the once-daily arm, two patients complained of fatigue, but not during twice-daily therapy. Despite the inconvenience of the second injection, 12/17 patients preferred the double-daily dosing of PTH [20].

Subsequently, Winer et al. conducted a 3-year, randomized, open-label crossover study to establish the long-term efficacy of twice-daily rhPTH (1-34) compared with conventional treatment in 27 adults and 12 children affected by chronic hypoparathyroidism [21,22]. In adults, transient episodes of upper and lower extremity cramping, numbness, and tingling occurred unpredictably during both treatment arms, often without apparent fluctuation in serum calcium levels. There was no significant difference in the incidence of adverse events, such as neuromuscular irritability, bone pain, fatigue, or arthralgias. In seven subjects receiving rhPTH (1-34) and three subjects receiving calcitriol therapy, mild intermittent lower extremity bone pain occurred. Several patients reported less fatigue and greater endurance with rhPTH (1-34), whereas fatigue was a common complaint in the calcitriol group [20]. Children receiving rhPTH (1-34) over 3 years had stable renal function and normal linear growth and bone accrual. Analysis of symptom occurrence at any time during the follow-up showed no significant differences between groups. Serious adverse events included hypocalcemia on two occasions in a patient with CaSR activating mutation. During the study, there was a single report of bone pain from one child receiving rhPTH (1–34) [1–22,34].

Recently, rhPTH (1-34) was administered as a continuous infusion by the use of an insulin pump with multi micropulses release of the peptide, in order to mimic physiologic PTH secretion [23–25]. Winer et al. compared a pump

Table 3. The major findings regarding effects on serum and urinary calcium levels and reduction of calcium and calcitriol supplementation of all clinical studies conducted with rhPTH (1-34).

Authors and year of publication	Subjects	Type of study	Duration of the study	Main results
Winer et al. 1998 [20]	17 adults	Randomized, open-label crossover once-daily rhPTH (1-34) subcutaneous (s.c.) injections (46 ± 32 μg) versus twice-daily rhPTH 1-34 s.c. (97 ± 60 μg)	28 weeks	During the second half of the day (12–24 h), twice-daily rhPTH (1-34) increased serum calcium levels more effectively than once-daily rhPTH (1-34).
Winer et al. 2003 [21]	27 adults	Randomized, open-label crossover, twice-daily rhPTH (1-34) s.c. injections (37 ± 2.6 μg) versus calcium and 1-25$(OH)_2$ D	3 years	Throughout the 3-year study period, serum calcium levels were similar in both treatment groups within or just below the normal range. Mean urinary calcium excretion was within the normal range from 1 to 3 years in rhPTH (1-34)-treated patients, but remained above normal in the calcitriol group
Winer et al. 2010 [22]	12 children	Randomized, open-label, twice-daily rhPTH (1-34) s.c. injections (0.6 ± 0.5 μg) versus calcium and 1-25$(OH)_2$ D	3 years	Mean predose serum calcium levels were maintained at, or just below, the normal range, and urine calcium levels remained in the normal range throughout the 3-year study, with no significant differences between treatment groups.
Winer et al. 2012 [23]	8 adults	Open-label crossover via pump rhPTH (1-34) s.c. injections (13 ± 4 μg/d) versus twice-daily rhPTH 1-34 s.c. injections (37 ± 14 μg/d)	24 weeks	Pump versus twice-daily delivery of rhPTH (1-34) produced less fluctuation in serum calcium levels, a more than 50% reduction in urine calcium levels, and a 65% reduction in the PTH dose to maintain normal serum calcium levels
Winer et al. 2014 [24]	12 children and adults	Randomized, open-label crossover via pump rhPTH (1-34) s.c. injections (0.32 μg/Kg/d) versus twice-daily rhPTH 1-34 s.c. injections (0.85 μg/Kg/d)	13 weeks	rhPTH (1-34) delivered via pump produced near normalization of mean serum calcium, and normalized mean urine calcium excretion. Serum and urine calcium showed a biphasic pattern during twice-daily injection versus minimal fluctuation during pump delivery. The rhPTH (1-34) dosage was markedly reduced during pump delivery
Santonati et al. 2015 [26]	42 adults	Prospective, open-label study, once-daily rhPTH (1-34) 20 μg s.c. injections	2 years	Decrease of total dose of calcium and calcitriol supplementation. Serum calcium concentration remained stable in the normal range. The daily urinary excretion of calcium increased slightly, but not significantly, after 3 months of therapy, and then it returned to baseline values

delivery system with twice-daily injections to further refine replacement therapy with PTH (1-34) in adults and in children [23,24].

The first study analyzed eight adult patients with postsurgical chronic hypoparathyroidism in a 6-month, open-label, randomized, crossover trial. During this study, no serious adverse events occurred. Between pump and twice-daily delivery, mean frequency and severity of hypocalcemic symptoms did not differ significantly, and the frequency and severity of symptoms were higher at baseline than during the two study periods. Fatigue was also significantly greater between baseline and pump delivery. At the end of the study, seven of eight patients preferred pump to twice-daily delivery [23].

In another trial, the same group compared pump delivery with twice-daily injections of rhPTH [1–34] in 12 children and young adults with chronic hypoparathyroidism due to autoimmune polyendocrine syndrome type 1 or CaSR mutation. There were no episodes of severe tetany or seizures and no severe hypocalcemia (or hypercalcemia) requiring emergency treatment. At the conclusion of the study, some patients reported preference for pump delivery because of reduced symptoms associated with calcium fluctuations, ease of use, and the potential long-term health benefits [24].

rhPTH [1–34] treatment, administered by twice-daily subcutaneous injections, versus conventional therapy, produced a significant increase in markers of bone turnover [21]. Mean serum alkaline phosphatase and osteocalcin levels and mean urinary deoxypyridinoline and pyridinoline excretion levels were significantly higher throughout the 3-year study period in the PTH-treated group of adult patients affected by chronic hypoparathyroidism [21]. Subsequently, at year 3, serum osteocalcin and urinary pyridinium cross-links showed an apparent decrease compared with the values at year 2.5 [21]. Bone mineral content and BMD showed no significant between-group differences over the 3-year study period. On the other hand, the studies on use of pump delivery showed that bone turnover markers reduced significantly compared with twice-daily delivery [23,24]. No data exist regarding bone quality and risk of fracture and treatment with rhPTH (1–34) in hypoparathyroid patients.

Recently, a 2-year prospective, open-label study investigated the effects of 6 months of rhPTH (1–34) treatment (twice-daily 20 mcg daily) in 42 adult subjects with postsurgical hypoparathyroidism, as well as evaluating quality of life changes [26]. The mean serum calcium levels significantly increased from baseline to 15 days and remained stable until the end of the study, despite a significant reduction in calcium and vitamin D supplementation. Data derived by RAND SF-36 Health Survey showed a significant improvement in the mean scores of all eight domains at the

end of the study, but this study did not have a control group [26].

Regarding immunogenicity, in a clinical trial conducted in women with osteoporosis, antibodies that cross-reacted with rhPTH (1-34) were detected in 3% of women (15/541) treated with this drug. Antibodies were usually first detected following 12 months of treatment and diminished after withdrawal from therapy. No hypersensitivity reactions or allergic reactions among these patients were described, and antibody formation did not appear to have effects on serum calcium, or on BMD response [27].

2.3. Risk of osteosarcoma

The occurrence of osteosarcoma has been described in a study on rats treated with PTH given subcutaneously at doses of 10, 50, and 150 µg/Kg/day [28]. The doses of PTH were, respectively, 3–71 times higher than systemic exposure described in humans following a subcutaneous dose of 100 µg/day based on AUC. Moreover, bone metabolism in the rat differs from that in humans, and the different physiology may account for the increased incidence of osteosarcoma in rats [29]. With over 10 years of clinical post-approval experience with rhPTH (1–34) and 7 years with rhPTH (1-84) for treatment of osteoporosis, no adverse signals of osteosarcoma have been reported [29,30]. No skeletal malignancies have been described by clinical trials with cumulative numbers of 16,000 subjects treated with up to 3 years of continuous therapy [31–33].

3. Conclusions

In summary, regarding data on the safety of rhPTH (1-84), the pivotal trial REPLACE has not shown significant differences between the PTH group and the placebo group in mean cardiovascular variables, including blood pressure, heart rate, or QTc (corrected QT) interval, or renal variables, such as serum creatinine or estimated creatinine clearance with this therapy [12]. Compliance with injection was excellent for both groups. Despite substantial decreases in supplemental calcium and vitamin D requirements, rhPTH (1-84) was associated with fewer clinical symptoms of hypocalcemia during maintenance than was placebo. Only one serious adverse event in the PTH group, characterized by hypercalcemia requiring a brief hospital stay, was regarded as treatment-related. Subsequently, the extension study REPEAT did not show serious adverse events [13]. Finally, the longest experience with the therapeutic use of rhPTH (1-84) for 6 years demonstrated, although in a small sample, safety regarding the control of calcium homeostasis, without severe hypercalcemic or hypocalcemic events [14]. Regarding fracture events reported, it is unknown whether the fractures that have been observed are part of the natural history of hypoparathyroidism or attributable to rhPTH (1-84) treatment. Data on comorbidities, such as risk of fractures in patients with chronic hypoparathyroidism, are sparse. However, a recent Danish case finding study identifying patients with postsurgical hypoparathyroidism showed that hypoparathyroid patients did not have an increased risk of fracture compared with controls [34]. On the other hand, another study observed, in a cohort of 104 patients with idiopathic hypoparathyroidism and 64 healthy controls, that vertebral fractures occurred in 18.3% patients with idiopathic hypoparathyroidism and in 4.7% of controls. Despite increased BMD, prevalence of vertebral fractures was higher in patients with idiopathic hypoparathyroidism [35]. Therefore, further data regarding risk of fractures in hypoparathyroid patients are necessary. It is known that chronic hypoparathyroidism is a state of low bone turnover with an increased BMD. This particular state is 'reversed' by administration of rhPTH (1-84), causing a marked increase in bone turnover with an increased number of Haversian canals per unit area in cortical bone, and a decreased trabecular thickness and trabecular bone tissue density. Moreover, a higher connectivity density in trabecular bone, as evaluated by micro-computed tomography performed on iliac crest bone biopsies of patients with hypoparathyroidism into 24 weeks of treatment with rhPTH (1-84) 100 µg/day compared to placebo, and an increased trabecular volumetric BMD, as assessed by quantitative computed tomography were described. In some patients, rhPTH (1-84) treatment causes trabecular tunneling [36]. The decrease of BMD described at the distal one-third radius is compatible with the known effects of PTH to increase cortical porosity and endosteal resorption, but it is possible that salutary effects on microarchitecture and bone size could provide biomechanical advantages at cortical bone [14]. It can be hypothesized that the marked increase in bone turnover may induce a renewal of the overmineralized bone that is typically described in case of chronic hypoparathyroidism; however, further investigation on the effects of long-term treatment with PTH replacement therapy in patients with hypoparathyroidism on bone is needed to determine effects on bone quality and strength. In this regard, more data are also needed from long-term bone biopsies in order to understand the real implications of the BMD changes.

Currently, rhPTH (1-84) is available through a restricted program under a Risk Evaluation and Mitigation Strategy and carries a 'black box warning.' It is unknown whether long-term therapy may also cause osteosarcoma in humans, but because of a potential risk, rhPTH (1-84) is only recommended for use in patients whose hypocalcemia cannot be controlled by calcium supplementation and active forms of vitamin D, and for whom the potential benefits are considered to outweigh this potential risk [6].

Finally, the studies on subcutaneous injections twice a day of rhPTH (1–34) have shown good control of calcium concentrations compared with conventional therapy, and less fluctuations in serum calcium levels compared with injections once a day [20–22]. However, so far, injections once- or twice-a-day therapy with rhPTH (1-34) have not been shown to be able to induce a significant reduction in 24-h urinary calcium compared to conventional therapy. The studies, conducted for 3 years to establish the long-term efficacy of twice-daily rhPTH [1–34] compared with conventional treatment, in 27 adults and 12 children affected by hypoparathyroidism, did not show significant differences in the incidence of adverse events, between both treatment arms, and compared with the group treated with conventional therapy produced a significant increase in markers of bone turnover [21,22]. The study with rhPTH (1-34) therapy delivered by an infusion pump showed near normalization of the diurnal rhythm of

PTH, calcium, phosphate concentrations, and markers of bone turnover, and a significant reduction of 24-h urinary calcium levels compared with twice-a-day injection therapy with rhPTH (1-34) [24]. No episodes of severe tetany or seizures and no severe hypocalcemia (or hypercalcemia) requiring emergency treatment during the study were described [24]. No studies have reported the development of skeletal malignancies. Further studies on the effect of therapy with rhPTH (1-34) on BMD changes, bone quality, and risk of fracture should be performed.

4. Expert opinion

Research done in this field so far has shown that replacement treatment with rhPTH is an attractive option for subjects affected by chronic hypoparathyroidism who are unable to maintain stable and safe serum and urinary calcium levels. Both rhPTH (1-84), administered by injection once a day, and rhPTH (1-34), especially delivered by an infusion pump, reduce the supplementation of calcium and vitamin D required, maintaining normal serum calcium. However, rhPTH (1-34)] has not been approved by the FDA for treatment of chronic hypoparathyroidism. rhPTH (1-84) can be considered more attractive than rhPTH (1-34) as a replacement hormone therapy, because the full-length peptide is exactly what is missing in this disease, and its effective half-life is longer than rhPTH (1-34). Moreover, the studies on rhPTH (1-84) for treatment of hypoparathyroidism have been conducted with a longer duration and with more patients compared with studies conducted with rhPTH (1-34). The FDA approval of rhPTH (1-84) in the USA is an important step in the new therapeutic management of this disease, which sometimes presents very difficult therapeutic clinical management. Data in cohorts of subjects treated with rhPTH (1-84) for 4–6 years [11,14] have not raised any safety concerns, although additional long-term data are necessary.

The risk of osteosarcoma will have to be analyzed and monitored in the next long-term studies of chronic treatment with rhPTH (1-84), though the use of rhPTH (1-34), introduced as a treatment for osteoporosis in 2002, has not yet revealed information that might suggest a higher risk of this tumor compared to the general population, as well as the longest experience with the therapeutic use of rhPTH (1–84) of 6 years. During the first few months of treatment with rhPTH, hypercalcemia can occur, but it is readily corrected with titration of the patient's supplementation regimen, therefore, this does not appear to be an important issue for this type of treatment. Many adverse events, including nausea, headache, musculoskeletal ache, fatigue, dizziness, neurologic, mental and mood alterations, paresthesia, and increased urination, tend to decrease during treatment with rhPTH (1-84) [14]. Moreover, studies usually show good compliance, optimal tolerance, and high tolerance to the drug (1-84). However, since therapy with rhPTH is a long-term management option in hypoparathyroidism, more long-term safety data are needed.

In the coming years, further studies are needed regarding the effects of rhPTH therapy on hypercalciuria and clinically relevant renal complications, such as renal impairment, nephrocalcinosis and nephrolithiasis, or other ectopic calcifications. In addition, the long-term effect on BMD, bone quality, and the risk of bone fractures must be clarified. Other delivery systems of rhPTH, not requiring subcutaneous injection, could be investigated to further increase patient compliance to therapy. Moreover, studies regarding more physiologic delivery systems and ideal dosing could be useful, because therapies with rhPTH still cannot exactly mimic the physiological PTH levels and calcium-phosphate homeostasis. Moreover, doses of rhPTH should be graded according to age/weight of the patient and, above all, based on the therapeutic response, in order to avoid, as much as possible, physiological fluctuations in levels of PTH, calcium, and phosphorus. Regarding the effects of rhPTH (1-84) on quality of life, in literature, there are limited and conflicting data with each other [15,16], thus, further placebo-controlled studies should be conducted to analyze this aspect on large samples and with long follow-up. Probably, adequate and specific questionnaires should be created to assess accurately all aspects involved in quality of life of these patients.

Future trials with rhPTH in children with developing skeletons affected by chronic hypoparathyroidism are necessary. In addition, future clinical studies will have to determine whether subjects aged 65 and over respond to treatment with rhPTH in a different manner than younger subjects.

Finally, long-term studies on rhPTH (1–34) are necessary, like those that have been conducted for rhPTH (1-84), and a study that compares both drugs could clarify the differences between them.

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